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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/781,296	01/13/1997	JOHN B. HARLEY	OMRF161	8073

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EXAMINER
CLOW, LORI A

ART UNIT	PAPER NUMBER
1631	42

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/781,296	Applicant(s) HARLEY ET AL.	
	Examiner Lori A. Clow, Ph.D.	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

In view of the appeal filed on 22 January 2002, PROSECUTION IS HEREBY REOPENED.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) File a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) Request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Should appellant elect to continue the appeal, the following defects in the appeal must be corrected:

(1) The status of the pending claims is incorrect. Claims 27-40 are NOT on appeal. The invention on appeal only relates to pending claims 27-29.

(2) Claims 30-40 are non-elected and therefore the groups stated as peptides of defined amino acids (claims 27, 29-34) and methods of administration (claims 28, 35-40) are drawn to a non-elected inventions and are improper because the arguments in appellants brief pertain to all claims and not just those on appeal.

Claims Rejections-35 USC 112

Claims 28 and 29 remain rejected under 35 U.S.C.112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection. As stated in the previous office action, the field of autoimmunity is unpredictable and therefore, one of ordinary skill in the art would not be able to extrapolate from the limited examples the scope of the variety of peptides, dosages, and dosing schedules in order to find tolerance inducing regimes.

Furthermore, while any given specific peptide administered prior to EBV infection might elicit tolerance to EBV effects associated with that specific peptide, there is nothing to suggest that tolerance to an "epitope" of EBV confers tolerance to ALL epitopes. A patient may have an immune response to any one of the numerous epitopes associated with the EBV virus and the specification fails to point to this issue. Appellant's arguments are not persuasive in that *In re Wands* sets forth that the following factors shall be taken into consideration when assessing undue experimentation:

(a) The breadth of the claims;

(b) The nature of the invention;

(c) The state of the prior art;

(d) The level of one of ordinary skill;

(e) The level of predictability in the art;

(f) The amount of direction provided by the inventor;

(g) The existence of working examples and;

(h) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In the instant case, appellant has failed to provide working examples in such that a person of ordinary skill in the art could make or use the invention. Simply stating that the peptides CAN be used therapeutically and that they CAN be administered in an EFFECTIVE dose, as stated on page 24 of the disclosure, does not teach the proper mode or dose to administer in order to practice the invention. The examples shown are not within the scope of the instant claims. The instant claims read upon administration of peptide(s) to elicit tolerance to EBV that is associated with a particular peptide. However, nothing suggests tolerance to an epitope of EBV that would confer tolerance to all epitopes. As echoed by Van Regenmortel (Vaccine, vol.19:2369-2374 (2001)) measurements of concentration, specificity, and affinity of antibodies or of the strength of the cytotoxic lymphocyte response induced by a vaccine, are, at best, surrogate assays that still need to be validated in protection trials (page 2371). Antibodies are always polyspecific and, in addition to recognizing the epitope against which it was elicited, an antibody will always bind to a variety of structurally related or unrelated epitopes (page 2372). Thus, barring evidence to the contrary, tolerance to one peptide does not suggest tolerance to all peptides. In fact, it is well known in the art that the generation of Th and Tc cells to several epitopes is fundamental in overcoming the variation in the immune response in the population due to MHC polymorphisms. Appellant's specification actually states that there are many known autoantigens associated with SLE and that there is no one that defines the disease (page 37). Therefore, in order for an effective memory response, several peptide combinations would have to be tested extensively in order to assess efficacy. This is well beyond the scope of the instant application.

The specification does not set forth any direct correlation between the administration of the elected composition and the development of tolerance to EBV associated immune responses. While antibodies to a particular epitope could be common in a patient with SLE, there is no indication that the administration of a single epitope would have any effect upon the clinical course of the disease. It is also unclear from the specification if the administration of the claimed composition would prevent the development of antibodies to other autoantigen epitopes when challenged with native virus. The specification fails to even teach testing for autoantibody levels of other antigens.

Furthermore, the declaration under 37 CFR 1.132 filed 05 February 1999, has been considered and is not deemed persuasive for reasons set forth in the previous office action and re-iterated herein. In order to measure tolerance, the lack of subsequent production of a relevant autoantibody to that peptide was monitored. However, there is no indication that immunization with one peptide tolerizes a subject to a plurality of autoantibody inducing epitopes on the EBNA molecule, or other EBV antigenic portion. Nor is there any scientific basis for expecting that a single epitope will confer tolerance to other non-overlapping epitopes. The claims are NOT limited to a particular dosing schedule or condition, as set forth in the declaration, which apparently do have an effect upon tolerance induction to that antigen. The claims are further not limited to induction of tolerance to a sole epitope. Furthermore, it is known that a single immunoglobulin molecule consists of many different combining sites. This leads to many potential cross-reactivities between related and unrelated antigenic determinants or epitopes.

The specification does not provide any direct correlation between the administration of the elected compositions and the development of tolerance to EBV associated immune

responses. Antibodies to particular epitopes could be common in SLE patients, however, there is no indication that the administration of a SINGLE epitope would have an effect upon the clinical course of the disease. It is also not clear that the administration of the claimed composition would prevent development of antibodies to other autoantigen epitopes. Claim 27 presents several epitopes, however, it is not clear that a vaccine with just one epitope would prevent patient from developing antibodies to a different epitope upon challenge with the native virus.

Therefore, the specification is NOT enabling for the invention as now claimed.

Claims 27-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 27-29 recite peptide compositions comprising peptide molecules selected from the group consisting of SEQ ID Nos 1, 2, 3 etc...and combinations thereof wherein the peptide comprises up to about forty amino acids and is present either in free form or bound to a carrier molecule. However, none of the peptides in the Markush group have 40 amino acids. This is confusing and the claim language would seem to suggest that the peptides in said group could have additional amino acids added to them.

Claim 28 recites [...and combinations or immunogenic portions thereof...] which was introduced in the October 18, 1999 (certificate of mailing date) amendment. This is considered new matter, as there is no basis in the specification for "immunogenic portion". Appellant is invited to point to where specific support exists in the disclosure.

Furthermore, SEQ ID NO. 24 is not disclosed in the parent application 08/160,604 for the simple and clear fact that the instant application claims a peptide with 9 amino acids. However, the parent application explores only octapeptides. Appellant is requested to provide evidence that eight does in fact equal nine. Appellant's arguments in the appeal brief at page 22-23 are disingenuous because they fail to point out that SEQ ID NO. 24 is a nonomer in actuality and not an octamer. Appellant's statement that "figures 7A and 7B are the immunoreactivity of octapeptides of the Ro antigen..." is inaccurate as SEQ ID NO. 24 is a nonapeptide asserted to contain the reactive octamer.

Claims Rejections-35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 27 remains rejected under 35 USC 102(b) as being clearly anticipated by SEQ ID NO. 4 of Middeldorp (WO 94/06912) and the disclosure of amino acids 430-438.

Claim 27 remains rejected under 35 USC 102(e) as being clearly anticipated by (US 5,965,353) for reasons set forth in the previous office action.

Claims 27-29 are rejected under 35 USC 102(e) as being anticipated by Harley et al. (US 6,232,522) for disclosing the exact invention (peptide compositions) as the instant application (see SEQ ID listings beginning with column 27).

35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

In response to applicant's argument that the prior art does not suggest the claimed invention because there is nothing in Middeldorp that would lead one to identify peptide sequences which are more immunoreactive with autoantibodies and that Middeldorp only discloses methods for vaccinating against EBV, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process

of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). Therefore, because the instant specification fails to point out exactly how appellant would administer and specifically utilize the claimed peptides the peptide disclosed in Middeldorp are interpreted as the same peptides as intended for use by appellant.

Middeldorp (US 5,965,353) discloses the exact peptide recited in claims 28 and 29 and discloses the treatment of EBV-related disease with those peptides (column 4, lines 59-64). Pharmaceutical preparations of the peptides are also contemplated. Middeldorp also specifically includes the use of fragments of the peptides which are disclosed at column 5, line 36 to column 6, line 15, which includes the peptide which is identical to the instant SEQ ID NO: 24. By immunizing the subject with a peptide, one tolerizes the subject to the effects of said peptide. Therefore, the suggestion of Middeldorp to immunize with peptides or fragments of SEQ ID Nos. 1 and 6, renders the claimed invention *prima facie* obvious, barring evidence to the contrary.

No claims are allowed.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242, or (703) 308-4028.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday-Friday from 10am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst, Bill Phillips, whose telephone number is (703) 305-3419, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

July 10, 2002

Lori A. Clow, Ph.D.
Art Unit 1631

Lori A Clow

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